

Effect of intermittent preventive treatment of malaria on health and education in schoolchildren: a cluster-randomised, double-blind, placebo-controlled trial

Siân E Clarke, Matthew C H Jukes, J Kiambo Njagi, Lincoln Khasakhala, Bonnie Cundill, Julius Otido, Christopher Crudder, Benson B A Estambale, Simon Brooker

Summary

Background Malaria is a major cause of morbidity and mortality in early childhood, yet its consequences for health and education during the school-age years remain poorly understood. We examined the effect of intermittent preventive treatment (IPT) in reducing anaemia and improving classroom attention and educational achievement in semi-immune schoolchildren in an area of high perennial transmission.

Methods A stratified, cluster-randomised, double-blind, placebo-controlled trial of IPT was done in 30 primary schools in western Kenya. Schools were randomly assigned to treatment (sulfadoxine-pyrimethamine in combination with amodiaquine or dual placebo) by use of a computer-generated list. Children aged 5–18 years received three treatments at 4-month intervals (IPT $n=3535$, placebo $n=3223$). The primary endpoint was the prevalence of anaemia, defined as a haemoglobin concentration below 110 g/L. This outcome was assessed through cross-sectional surveys 12 months post-intervention. Analysis was by both intention to treat, excluding children with missing data, and per protocol. This study is registered with ClinicalTrials.gov, number NCT00142246.

Findings 2604 children in the IPT group and 2302 in the placebo group were included in the intention-to-treat analysis of the primary outcome; the main reason for exclusion was loss to follow-up. Prevalence of anaemia at 12 months averaged 6·3% in the IPT group and 12·6% in the placebo group (adjusted risk ratio 0·52, 95% CI 0·29–0·93; $p=0·028$). Significant improvements were also seen in two of the class-based tests of sustained attention, with a mean increase in code transmission test score of 6·05 (95% CI 2·83–9·27; $p=0·0007$) and counting sounds test score of 1·80 (0·19–3·41; $p=0·03$), compared with controls. No effect was shown for inattentive or hyperactive-compulsive behaviours or on educational achievement. The per-protocol analysis yielded similar results. 23 serious adverse events were reported within 28 days of any treatment (19 in the IPT group and four in the placebo group); the main side-effects were problems of balance, dizziness, feeling faint, nausea, and/or vomiting shortly after treatment.

Interpretation IPT of malaria improves the health and cognitive ability of semi-immune schoolchildren. Effective malaria interventions could be a valuable addition to school health programmes.

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Introduction

Children living in areas of high malaria transmission rapidly acquire immunity to malaria in early childhood; by the time they reach school age, the risk of clinical attacks and death has reduced.^{1–3} However, many school-aged children continue to harbour asymptomatic parasitaemia, which can cause anaemia.⁴ Although malaria might have an adverse effect on cognition and education outcomes, evidence for this has so far been lacking,^{5,6} and the case for school-based malaria control has not been established.^{7–9} Historically, malaria chemoprophylaxis given to African schoolchildren was associated with lower rates of malaria parasitaemia and severe anaemia, fewer clinical attacks and malaria deaths,^{10,11} and reduced school absenteeism because of malaria.¹² One randomised trial has investigated the

effect of clinical malaria on educational outcomes and provides evidence that school performance is related to the cumulative effect of previous malaria attacks¹³ and that weekly chemoprophylaxis with chloroquine can improve school examination scores in Sri Lankan children.¹⁴ However, this approach faces operational challenges,¹⁵ and could prove less effective in sub-Saharan Africa, where subclinical infections predominate. An alternative strategy is intermittent preventive treatment (IPT), which involves the periodic mass administration of a full therapeutic course of an antimalarial drug, irrespective of infection status. We undertook a randomised controlled trial in western Kenya to investigate the efficacy of school-based IPT in reducing anaemia and improving classroom attention and educational achievement.

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London School of Hygiene and Tropical Medicine, London, UK (S E Clarke PhD, B Cundill MSc, C Crudder MSc, S Brooker DPhil); Harvard University, Cambridge, MA, USA (M C H Jukes DPhil); Division of Malaria Control, Ministry of Health, Nairobi, Kenya (J K Njagi PhD); African Mental Health Foundation, Nairobi, Kenya (L Khasakhala PhD); Institute of Tropical and Infectious Diseases, University of Nairobi, Kenya (J Otido MD, Prof B B A Estambale MD); and Malaria Public Health and Epidemiology Group, Centre for Geographic Medicine Research–Coast, KEMRI–Wellcome Trust Collaborative Programme, Nairobi, Kenya (S Brooker)

Correspondence to: Dr Siân Clarke, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
sian.clarke@lshtm.ac.uk

Methods

Participants

This stratified, cluster-randomised, double-blind, placebo-controlled trial was done between March, 2005, and March, 2006, in primary schools in Bondo district, western Kenya. Malaria transmission is intense and perennial in this region, with two seasonal peaks (March–May and November–December).¹⁶ By school age, clinical incidence declines to 0·25 episodes per child per year, although up to 50% of schoolchildren have asymptomatic malaria parasitaemia.^{2,3}

Rural primary schools with 150 children or more, and over 15 children per class were eligible for inclusion. Schools located within 5 km from Lake Victoria were excluded to minimise confounding by *Schistosoma mansoni*.¹⁷ Meetings were held in participating schools to explain the nature and purpose of the trial to parents or legal guardians, and written informed consent was obtained. Schoolchildren with parental consent and no history of adverse reaction to sulfa-based drugs were eligible for recruitment. Children with a haemoglobin concentration of less than 70 g/L at baseline, or known or

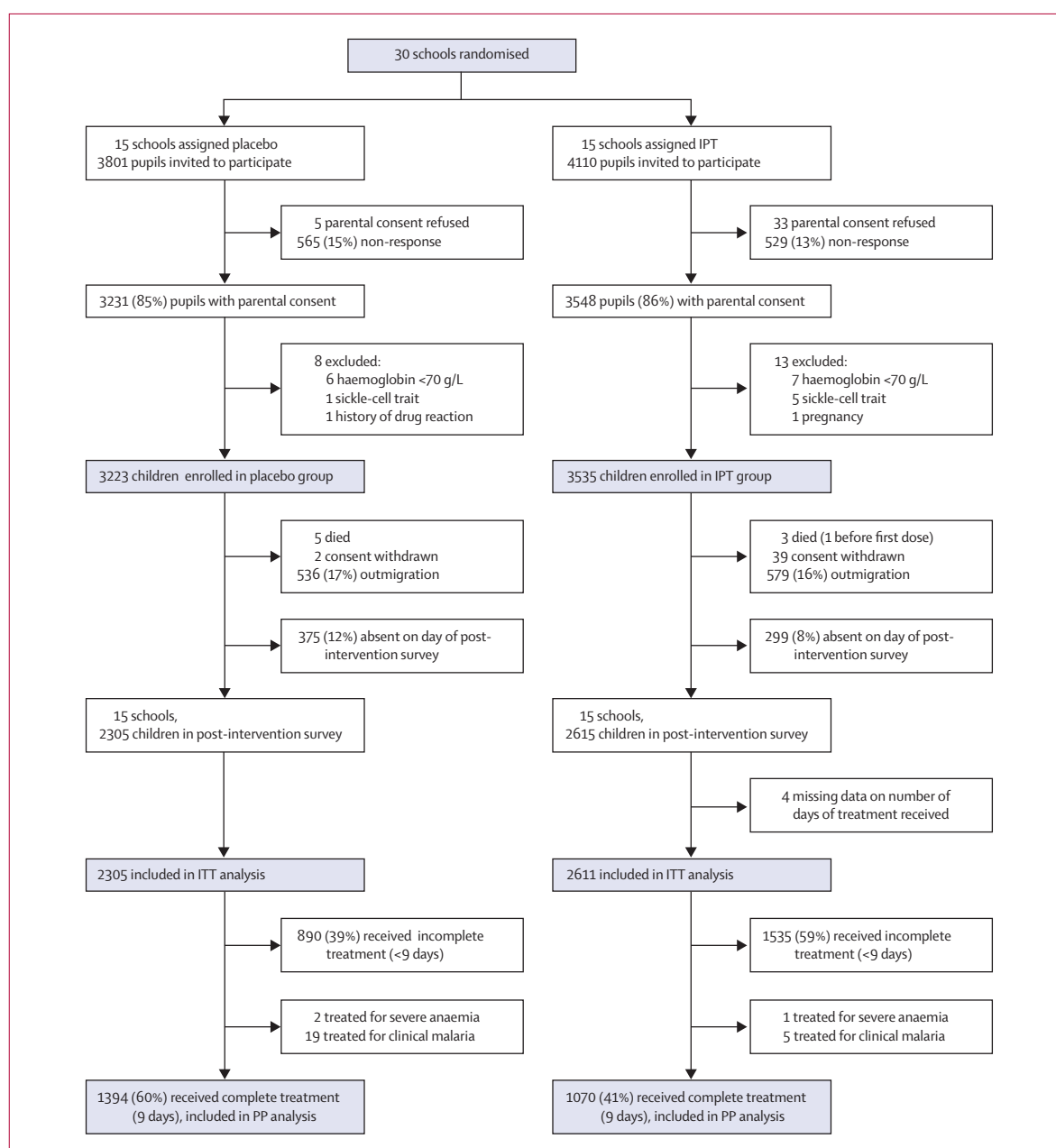


Figure 1: Trial profile

ITT=intention-to-treat. PP=per-protocol.

suspected to be homozygous for sickle-cell trait or pregnant were not enrolled.

The protocol was approved by the ethics review boards of Kenyatta National Hospital, Kenya; London School of Hygiene and Tropical Medicine, UK; and Danish National Committee on Medical Research Ethics, Denmark. Permissions were obtained from the Kenyan Ministry of Education, the District Education and Health Authorities, and head teachers. An independent data safety monitoring board monitored the trial and approved the analysis plan.

Procedures

We stratified schools into three groups according to school examination performance in previous years, to account for differences in school quality and socioeconomic environment. Ten schools were randomly selected from each school-performance stratum, and within each stratum schools were randomly allocated to one of six coded drug groups by use of block randomisation (three pairs of either active drugs or dual placebo) according to a computer-generated random number list by an investigator (SEC) blind to drug group.

Children in intervention schools received IPT with one dose of sulfadoxine-pyrimethamine and three daily doses of amodiaquine on three occasions within a 12-month period (once each school term). IPT was first given in May, 2005, coinciding with a seasonal peak in transmission, and then repeated in September, 2005, and January, 2006. Children absent from school were not treated. Children in control schools received dual placebo tablets over 3 consecutive days on each occasion.

Study drugs and placebos were manufactured by Cosmos Limited (Nairobi, Kenya) and labelled according to six coded drug groups. The code was held by the manufacturers and the data safety monitoring board, and revealed to the investigators only after completion of the statistical analysis. Dosage was by age. Participants were observed for 30 min after drug intake and treatment re-administered once more if spitting or vomiting occurred. Active drugs and placebos were similar in size and shape, but differed in taste. To preserve blinding, staff responsible for measuring health or education outcomes were unaware of drug group allocation, and analysis was done by a statistician with no previous involvement in the trial. Adverse events were monitored by the study team for 3 days after each treatment, and a further 28 days thereafter using a passive surveillance system in schools and local health centres. Travel costs were reimbursed and treatment charges waived. Adverse effects were monitored until the event was cured or had stabilised.

Incidence of clinical attacks was not measured, although a blood slide was prepared in children presenting with fever during school visits, and slide-

positive cases were treated for malaria in accordance with national guidelines. Children with a haemoglobin concentration less than 70 g/L were given a course of haematinics. *S. mansoni*-positive children received one dose of praziquantel (40 mg/kg). Children in all schools (intervention and placebo) received mass treatment twice a year for soil-transmitted helminth infections with one dose of albendazole (400 mg).

We investigated whether intermittent clearance of malaria parasitaemia would increase haemoglobin concentrations and, as a consequence, reduce anaemia and contribute to improved attention in class and educational performance. The primary endpoint was the prevalence of anaemia, defined as a haemoglobin concentration of less than 110 g/L, after 12 months of intervention. Secondary endpoints included prevalence and intensity of *Plasmodium falciparum* infection, mean haemoglobin concentration, sustained attention, and educational achievement.

Cross-sectional surveys were done in all schools in March, 2006, approximately 6 weeks after the last treatment. Finger-prick blood samples were obtained from all children with consent (aged 5–18 years) to assess haemoglobin concentration with a portable photometer (Hemocue, Angelholm, Sweden). Blood slides prepared for malaria were declared negative only after examination of 100 high-powered fields. Data on covariates, including bednet use and household socioeconomic status were obtained through a questionnaire administered to children in classes 2–7 (aged 7–17 years) during the final survey. Height and weight were measured, and anthropometric indices calculated. For logistical reasons, only children in classes 5 and 6 were asked to provide stool samples, which were examined microscopically for helminth eggs by use of the Kato-Katz technique.

The effect of the intervention on cognitive abilities was investigated primarily by comparing differences in test scores of sustained attention given to a cohort of children in classes 5 and 6 (aged 11–16 years). This group was selected for testing because they were old enough to understand the test instructions. Secondary education outcomes included behaviour in class and educational achievement.

Two tests of sustained attention were undertaken on the day preceding health assessments. Both tests were adapted from the TEA-Ch (tests of everyday attention for children) battery¹⁸ for group administration in groups of 15 or fewer, and given by a psychologist already trained in doing these tests. The tests involved listening to a tape and identifying different sounds (counting sounds) and numbers (code transmission). In the counting sounds tasks children were required to count a series of electronic beeps played on the tape recorder, with varying delays of 0·3–10 seconds between sounds. Sustained attention was required to keep track of the number of sounds counted during delays and to

	Intention-to-treat population		Per-protocol population	
	Placebo	IPT	Placebo	IPT
Number of children included in analysis	2305	2611	1394	1070
Mean age (years)	11.23 (3.09)	11.24 (3.05)	11.51 (2.92)	11.53 (2.85)
Sex (male)	1209/2305 (52%)	1405/2611 (54%)	708/1394 (51%)	559/1070 (52%)
History of residence in a non-malarious area	190/1952 (10%)	167/2221 (8%)	124/1239 (10%)	82/974 (8%)
Reported use of bednet by child	561/1952 (29%)	495/2215 (22%)	346/1239 (28%)	211/970 (22%)
Household ownership of bicycle	1434/1944 (74%)	1616/2222 (73%)	890/1232 (72%)	698/971 (72%)
House structure				
Traditional	654/1957 (33%)	745/2231 (33%)	406/1243 (33%)	321/977 (33%)
Semi-permanent	831/1957 (42%)	874/2231 (39%)	529/1243 (43%)	386/977 (40%)
Permanent	472/1957 (24%)	612/2231 (27%)	308/1243 (25%)	270/977 (28%)
Lighting				
Tin lamp only	1325/1956 (68%)	1400/2231 (63%)	839/1242 (68%)	624/976 (64%)
Hurricane lamp	577/1956 (29%)	747/2231 (33%)	369/1242 (30%)	308/976 (32%)
Electricity/other	54/1956 (3%)	84/2231 (4%)	34/1242 (3%)	44/976 (5%)
Family status				
Lives with guardian	421/1957 (22%)	437/2234 (20%)	260/1243 (21%)	217/977 (22%)
Lives with one parent	371/1957 (19%)	421/2234 (19%)	231/1243 (19%)	159/977 (16%)
Lives with both parents	1165/1957 (60%)	1369/2234 (61%)	752/1243 (60%)	601/977 (62%)
Parental education†				
No education	46/657 (7%)	59/711 (8%)	30/449 (7%)	32/346 (9%)
Primary education only	341/657 (52%)	359/711 (50%)	236/449 (53%)	171/346 (49%)
Secondary education	236/657 (36%)	253/711 (36%)	163/449 (36%)	121/346 (35%)
Higher education	34/657 (5%)	40/711 (6%)	20/449 (4%)	22/346 (6%)
Nutritional status at baseline‡				
Weight-for-age Z score	-1.62 (1.05)	-1.60 (1.11)	-1.65 (1.03)	-1.54 (1.08)
Height-for-age Z score	-1.68 (1.02)	-1.68 (1.12)	-1.67 (1.02)	-1.63 (1.10)
Helminth infection at follow-up§				
Hookworm	74/598 (12%)	82/612 (13%)	47/396 (12%)	34/272 (13%)
<i>Ascaris lumbricoides</i>	28/598 (5%)	32/612 (5%)	15/396 (4%)	9/272 (3%)
<i>Trichuris trichiura</i>	32/598 (5%)	52/612 (8%)	18/396 (5%)	23/272 (8%)
<i>Schistosoma mansoni</i>	59/598 (10%)	32/612 (5%)	29/396 (7%)	15/272 (6%)
Study endpoints at baseline†				
Number of children examined	1149	1330	748	637
<i>P. falciparum</i> prevalence	465/1113 (42%)	524/1284 (41%)	278/728 (38%)	243/612 (40%)
<i>P. falciparum</i> intensity per µL among slide-positive: geometric mean	1028.85 (1.30)	988.88 (1.18)	923.15 (1.26)	961.23 (1.14)
Anaemia prevalence	254/1145 (22%)	246/1326 (19%)	155/745 (21%)	104/636 (16%)
Mean haemoglobin concentration (g/L)	119.50 (15.54)	121.42 (14.47)	119.78 (15.27)	122.19 (14.13)

Data are mean (SD) or n/N (%) unless specified otherwise. *Data obtained at follow-up for all classes (5–18 years), apart from where indicated. †Measured at baseline among children who were enrolled in classes 5 and 6; also includes data for children in all classes in a randomly selected subset of 12 schools. ‡Anthropometric indices calculated on the basis of the 2000 Centers for Disease Control and Prevention growth charts. Weight-for-height standards were only available for children up to 121 cm in height and thus not calculated. Measured at baseline (ITT: 1141 placebo, 1321 IPT; PP: 744 placebo, 633 IPT). §Helminth infection was only measured among children enrolled in classes 5 and 6 at baseline.

Table 1: Characteristics of schoolchildren included in analyses of health outcomes*

be prepared for bursts of several consecutive sounds. In the code transmission tasks, a list of digits was read out aloud at the speed of one per second. Children were required to listen out for a “code”—two consecutive occurrences of the number 5—and then record the two numbers that preceded the code. A second test, included in the final survey, required children to recall the three numbers that preceded the code. Before each test

children were given a warm-up activity to familiarise them with the tape recorder, and three practice exercises. Internal reliability was high for both tests (Cronbach $\alpha > 0.7$ for counting sounds and $\alpha > 0.8$ for code transmission).

Classroom behaviour was assessed by teacher ratings of inattentive and hyperactive-impulsive behaviours in eight children randomly selected (by MCHJ) from each

class by use of a computer-generated random number list. Behaviours were selected from the early childhood attention deficit disorder scale.¹⁹ Behaviours that were weakly correlated (<0.3) with the sum of other behaviour scores in piloting were deemed not to be strongly related to the overall trait and were dropped from the final instrument. Internal reliability was high (Cronbach $\alpha > 0.8$). Assessment of educational achievement focused on learning which occurred towards the end of the intervention year, when the cumulative effect of repeated malaria treatment should have achieved maximum improvements in classroom attention. Knowledge of a content-based subject, taught during the last school term of the study, was measured in the two intervention groups. In January, 2006, teachers attended a 1-day training seminar to standardise the curriculum and teaching methods for social studies in classes 6 and 7. Children were tested at the end of the school term. A multiple choice exam was developed for each class. Internal reliability was adequate for both class exams (Cronbach $\alpha = 0.62$ for class 6 and $\alpha = 0.59$ for class 7).

Statistical analysis

On the basis of an observed anaemia prevalence of 38% at baseline and coefficient of variation between clusters of 0.27, a sample size of 12 schools with a total of 889 children in each arm was estimated to provide 80% power to detect a 30% reduction in the prevalence of anaemia in the intervention group compared with placebo at 5% level of significance.²⁰ For the cognitive and education tests, where an intraclass correlation of 0.20 was assumed, a minimum of 15 schools per arm with 60 children assessed per school were needed to provide 80% power to detect an effect size of 0.25 in the intervention group compared with placebo at 5% level of significance.

Data were analysed by intention to treat, excluding those children with missing data. A per-protocol analysis was also done, including only children treated on all three rounds and who completed the full 3-day regimen on each occasion, totalling 9 days of treatment. Children who received either haematinics for severe anaemia or active antimalarials for clinical malaria, or both, at any point during the study were excluded from the per-protocol analysis.

The effect of the intervention was analysed with methods appropriate for a cluster-randomised trial.²¹ The prevalence, or mean, in each school was calculated and the unadjusted risk ratio, or mean difference (intervention–control), estimated in each stratum. An overall estimate of the effect of IPT was obtained by taking a weighted average of the stratum-specific estimates, the weights proportional to the number of schools per stratum, and 95% CIs were adjusted for observed between-school variance (Hayes R, London School of Hygiene and Tropical Medicine, personal

	Intention-to-treat population		Per-protocol population	
	Placebo	IPT	Placebo	IPT
Number of children included in analysis	382	436	274	209
Mean age (years)	13.74 (1.17)	13.89 (1.19)	13.71 (1.18)	13.83 (1.17)
Sex (male)	196/382 (51%)	213/436 (49%)	134/274 (49%)	97/209 (46%)
History of residence in a non-malarious area	40/381 (10%)	47/435 (11%)	26/273 (10%)	25/208 (12%)
Reported use of bednet by child	73/380 (19%)	72/433 (17%)	51/272 (19%)	33/208 (16%)
Household ownership of bicycle	257/380 (68%)	290/433 (67%)	183/272 (67%)	136/208 (65%)
House structure				
Traditional	132/382 (35%)	153/435 (35%)	98/274 (36%)	66/208 (32%)
Semi-permanent	164/382 (43%)	151/435 (35%)	113/274 (41%)	74/208 (36%)
Permanent	86/382 (23%)	131/435 (30%)	63/274 (23%)	68/208 (33%)
Lighting				
Tin lamp only	268/382 (70%)	267/435 (61%)	193/274 (70%)	125/208 (60%)
Hurricane lamp	107/382 (28%)	152/435 (35%)	76/274 (28%)	72/208 (35%)
Electricity/other	7/382 (2%)	16/435 (4%)	5/274 (2%)	11/208 (5%)
Family status				
Lives with guardian	89/382 (23%)	94/433 (22%)	60/274 (22%)	47/207 (23%)
Lives with one parent	74/382 (19%)	93/433 (21%)	53/274 (19%)	39/207 (19%)
Lives with both parents	219/382 (57%)	246/433 (57%)	161/274 (59%)	121/207 (58%)
Parental education†				
No education	24/298 (8%)	31/315 (10%)	18/213 (8%)	16/144 (11%)
Primary education only	139/298 (47%)	158/315 (50%)	93/213 (44%)	68/144 (47%)
Secondary education	117/298 (39%)	111/315 (35%)	90/213 (42%)	51/144 (35%)
Higher education	18/298 (6%)	15/315 (5%)	12/213 (6%)	9/144 (6%)
Nutritional status at baseline†‡				
Weight-for-age Z score	−1.75 (1.07)	−1.65 (1.09)	−1.73 (1.07)	−1.58 (1.07)
Height-for-age Z score	−1.67 (0.98)	−1.63 (1.03)	−1.65 (0.99)	−1.62 (1.03)
Helminth infection at follow-up				
Hookworm	44/357 (12%)	45/387 (12%)	29/255 (11%)	23/192 (12%)
Ascaris lumbricoides	11/357 (3%)	21/387 (5%)	6/255 (2%)	7/192 (4%)
Trichuris trichiura	15/357 (4%)	36/387 (9%)	9/255 (4%)	17/192 (9%)
Schistosoma mansoni	28/357 (8%)	18/387 (5%)	14/255 (5%)	10/192 (5%)
Study endpoints at baseline†				
Number of children examined	361	416	261	201
<i>P. falciparum</i> prevalence	130/349 (37%)	139/406 (34%)	87/254 (34%)	72/195 (37%)
<i>P. falciparum</i> intensity per μ L in slide-positive: geometric mean	802.32 (1.19)	733.21 (1.14)	805.45 (1.11)	725.65 (1.12)
Anaemia prevalence	55/359 (15%)	44/416 (11%)	34/260 (13%)	24/201 (12%)
Mean haemoglobin concentration (g/L)	122.92 (15.26)	124.81 (13.92)	123.26 (14.57)	124.90 (14.06)
Mean score in counting sounds test§	11.19 (3.02)	11.25 (3.04)	11.12 (2.99)	11.08 (3.22)
Mean score in code transmission test§	13.03 (4.99)	13.31 (4.99)	13.11 (4.74)	13.47 (5.00)

Data are mean (SD) or n/N (%) unless specified otherwise. *Data obtained at follow-up for education cohort recruited from classes 5 and 6 (11–16 years), except where indicated. †Measured at baseline. ‡Anthropometric indices calculated on the basis of the 2000 Centers for Disease Control and Prevention growth charts. Weight-for-height standards were only available for children up to 121 cm in height and thus not calculated. Measured at baseline (ITT: 359 placebo, 415 IPT; PP: 260 placebo, 200 IPT). §Sustained attention tested at baseline (ITT: 345 placebo, 364 IPT; PP: 249 placebo, 178 IPT).

Table 2: Characteristics of schoolchildren included in analyses of education outcomes*

	Placebo	IPT
School exam performance in previous 3 years†‡		
Lowest tertile (stratum 1)	219.55 (219.48–220.25)	205.34 (204.34–217.76)
Middle tertile (stratum 2)	246.38 (245.96–249.23)	233.47 (232.43–235.05)
Upper tertile (stratum 3)	267.81 (266.95–272.32)	291.08 (277.63–296.91)
Mean number of children enrolled per school (classes 0–7)†		
School performance stratum 1	156.0 (44.20)	144.2 (50.25)
School performance stratum 2	214.6 (50.86)	250.8 (33.80)
School performance stratum 3	298.8 (161.06)	338.2 (124.12)
Quality of social science teaching during final term of intervention		
Teacher absenteeism		
Absent for >1 day	11 (73%)	10 (67%)
Number of days absent	3 days (2–8)	3.5 days (2–5)
Proportion of work completed and marked	0.16 (0.15)	0.14 (0.17)
Progression: number of lessons per week	4.25 (1.83)	6.33 (3.90)
Lesson plans: number of lesson plans per week	3.53 (2.83)	3.67 (3.29)
Number of teaching aids in use		
None	4 (27%)	5 (33%)
One	1 (7%)	2 (13%)
Two or more	10 (67%)	8 (53%)

Data are mean (SD), median (IQR), or n (%). *Intention-to-treat and per-protocol populations drawn from same set of 30 study schools (15 placebo, 15 IPT). †Five schools per strata in each treatment arm. ‡Median (IQR) of the mean pass rate in national primary school leaving exams (KCPE) during 3 years before intervention.

Table 3: Data on school level characteristics* for schoolchildren included in analyses of education outcomes

communication). Effect size for cognition was calculated by dividing the difference in the mean cluster-level summaries by the standard deviation of individual values averaged across study arms. Formal hypothesis testing was done with stratified unpaired *t* tests. Standard individual-level regression analysis, which incorporated stratum as a fixed effect and all covariates, suspected a priori to be confounders or effect modifiers, except the intervention effect, was used to calculate cluster-level expected values. Observed and expected values were compared by computing a residual, based on the ratio of observed to expected or the difference between observed and expected, for each school. Adjustment for covariates was undertaken replacing school-level means and proportions with covariate-adjusted residuals. Additionally, the effect of intervention was assessed with adjustment for baseline characteristics among those children for whom baseline data were available. All analyses were undertaken using STATA version 9.2.

This study is registered with ClinicalTrials.gov, number NCT00142246.

Role of the funding source

The sponsor of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. SEC, MCHJ, BC, and SB had full access to the data and made the final decision to submit for publication.

Results

The trial profile is shown in figure 1. 4916 (73%) of 6758 school children enrolled in the trial were examined in the post-intervention survey 12 months later. The numbers of children lost to follow-up were similar in IPT intervention and placebo schools (26% and 28%, respectively). Health outcomes for children in the intervention group (n=2611) and placebo group (n=2305) were analysed according to intention to treat. Most children examined post-intervention had received treatment on all three occasions (more than 7 days of treatment were completed by 1946 [75%] and 1990 [86%] in each group), although only 1070 (41%) of children in the intervention group and 1394 (60%) in the placebo group had received treatment on all 9 days and were included in the per-protocol analysis of health outcomes. Children lost to follow-up and those who received incomplete treatment had similar baseline characteristics to children included in the per-protocol analysis (table 1 and table 2). Children in the IPT intervention and placebo groups were similar, although those in the IPT intervention group had slightly better nutritional status at baseline and fewer children were anaemic. Imbalances in helminth infection at baseline were successfully corrected with anthelmintic mass treatment and no marked differences in prevalence of helminth infections existed between intervention and placebo groups at follow-up. 818 children (76% of the original education cohort in classes 5 and 6 at baseline) participated in the tests of sustained attention post-intervention (436 in the IPT group, 382 in the placebo group). Children lost to follow-up were similar to those examined post-intervention (data not shown). Study endpoints and nutritional status in the IPT and placebo groups were similar at baseline, with slight differences in socioeconomic background (table 2 and table 3).

At follow-up, the prevalence of anaemia among schoolchildren in the IPT intervention group was significantly lower than in the placebo group (table 4). Results of the intention-to-treat analysis show that the protective efficacy of the intervention against anaemia was 48% (95% CI 8–71; *p*=0.028; table 4). The adjusted risk difference was –0.06 (–0.01 to –0.11), equating to one case of anaemia prevented for every 16 children treated with IPT (95% CI 9–91 children). There were also fewer cases of severe anaemia (haemoglobin <70 g/L) in the IPT intervention group than in the placebo group (four and 16 cases, respectively). Similarly, post-intervention mean haemoglobin concentration was significantly higher among children in the intervention group than among controls (table 4; adjusted difference 5.01 g/L (95% CI 1.62–8.41; *p*=0.005). IPT seemed to benefit children across the whole distribution of haemoglobin concentrations, as shown by the different distributions between the two groups (figure 2). Prevalence of *P. falciparum* parasitaemia was lower

among children receiving IPT than in those in the placebo group, with a protective efficacy against *P falciparum* infection of 89% (95% CI 73–95; $p=0.0002$; table 4). The adjusted risk difference was -0.35 (0.30 to -0.41), equating to an average of one infection prevented for every three children treated with IPT

	Placebo		IPT		p value	Risk ratio/mean difference* (95% CI)
	Number of children	Outcome	Number of children	Outcome		
Intention-to-treat analysis†						
Prevalence of anaemia						
Crude‡	2302	12.6% (5.7–40.3%)	2604	6.3% (0.7–12.5%)	$p=0.041$	0.50 (0.26–0.97)
(Range between schools; $k=0.44$)						
Observed/expected: adjusted for strata§	2302	1.347	2604	0.689	$p=0.034$	0.51 (0.28–0.95)
Observed/expected: fully adjusted¶	2292	1.326	2599	0.689	$p=0.028$	0.52 (0.29–0.92)
Mean haemoglobin concentration (g/L)						
Crude‡	2302	124.5 (111.9–128.3)	2604	130.1 (123.7–138.4)	$p=0.002$	5.62 (2.19–9.05)
(Range between schools; $k=0.03$)						
Observed–expected: adjusted for strata§	2302	–2.94	2604	2.68	$p=0.002$	5.62 (2.19–9.05)
Observed–expected: fully adjusted¶	2292	–2.14	2599	2.88	$p=0.005$	5.01 (1.62–8.41)
Prevalence of <i>P falciparum</i> infection						
Crude‡	2294	39.7% (26.2–58.1%)	2584	4.6% (0.8–14.1%)	$p<0.0001$	0.12 (0.05–0.27)
(Range between schools; $k=0.14$)						
Observed/expected: adjusted for strata§	2294	1.949	2584	0.226	$p<0.0001$	0.12 (0.05–0.27)
Observed/expected: fully adjusted¶	1938	2.532	2182	0.286	$p=0.0002$	0.11 (0.05–0.27)
Intensity of <i>P falciparum</i> infection (per μL)**						
Crude‡	890	1282.5	104	2118.8	$p=0.255$	1.65 (0.68–4.01)
Observed–expected: adjusted for strata§	890	–0.254	104	0.248	$p=0.255$	1.65 (0.68–4.01)
Observed–expected: fully adjusted¶	699	0.315	74	1.013	$p=0.108$	2.01 (0.85–4.77)
Per-protocol analysis††						
Prevalence of anaemia						
Crude‡	1392	12.8% (5.5–36.4%)	1070	5.7% (0.17–9%)	$p=0.027$	0.44 (0.22–0.90)
(Range between schools; $k=0.44$)						
Observed/expected: adjusted for strata§	1392	1.369	1070	0.624	$p=0.027$	0.46 (0.23–0.91)
Observed/expected: fully adjusted¶	1387	1.351	1068	0.633	$p=0.025$	0.47 (0.24–0.90)
Mean haemoglobin concentration (g/L)						
Crude‡	1392	124.8 (114.9–128.5)	1070	130.7 (123.2–139.2)	$p=0.0010$	5.99 (2.70–9.28)
(Range between schools; $k=0.03$)						
Observed–expected: adjusted for strata§	1392	–2.90	1070	3.09	$p=0.0010$	5.99 (2.70–9.28)
Observed–expected: fully adjusted¶	1387	–2.32	1068	3.17	$p=0.0023$	5.49 (2.16–8.81)
Prevalence of <i>P falciparum</i> infection						
Crude‡	1386	39.3% (23.0–59.4%)	1059	3.7% (0.13–33%)	$p=0.0002$	0.10 (0.03–0.28)
(Range between schools; $k=0.18$)						
Observed/expected: adjusted for strata§	1386	1.709	1059	0.166	$p=0.0003$	0.10 (0.03–0.30)
Observed/expected: fully adjusted¶	1228	2.064	957	0.189	$p=0.0003$	0.09 (0.03–0.29)
Intensity of <i>P falciparum</i> infection (per μL)**						
Crude‡	530	1110.5	38	1262.2	$p=0.799$	1.14 (0.41–3.18)
Observed–expected: adjusted for strata§	530	–0.251	38	–0.123	$p=0.799$	1.14 (0.41–3.18)
Observed–expected: fully adjusted¶	444	0.101	32	0.210	$p=0.829$	1.12 (0.40–3.12)

Placebo and IPT intervention arms both contained 15 schools. *Risk ratios are presented for binary outcomes (anaemia and *P falciparum* occurrence), mean differences are presented for haemoglobin concentrations. Ratio of geometric means are presented for *P falciparum* intensity among those infected. †Intention-to-treat analysis: placebo $n=2305$, range 64–382 children per school; IPT $n=2611$, range 70–341 children per school. ‡Crude estimates account for the cluster-randomised trial design. Prevalence was calculated for each school, and the percentage shown represents the mean of these cluster-specific prevalence values. §Adjusted for stratified, cluster-randomised, trial design. ¶Fully adjusted for trial design, age, sex, age/sex interaction, and nutritional status. All covariates measured at follow-up. ||Fully adjusted for trial design, age, sex, age/sex interaction, bednet use, and migration history. All covariates measured at follow-up. **Geometric mean parasite density calculated in parasite-positive children only. ††Per-protocol analysis: placebo $n=1394$, range 33–171 children per school. IPT $n=1070$, range 24–165 children per school.

Table 4: Effect of IPT on health outcomes: anaemia, haemoglobin, and *P falciparum* parasitaemia

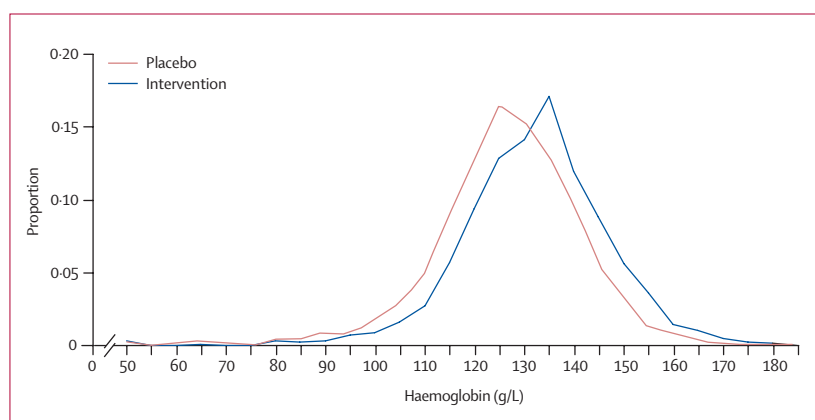


Figure 2: Distribution of haemoglobin concentrations among children, according to treatment (intention-to-treat population)

Individual-level data are presented; distribution does not take into account the clustering of children within schools.

(95% CI 2–4 children). Among the subset of children infected with *P falciparum* at follow-up, mean parasite density was similar in the two groups ($p=0.108$).

Results of the per-protocol analysis, which included only children who received complete treatment during each treatment round, were similar to those of the intention-to-treat analysis (table 4). Analysis was also repeated on the subgroup of 2471 children for whom haemoglobin data at baseline were available, and yielded similar results (data not shown), confirming that the observed differences are not attributable to slight baseline imbalances in nutritional status. Although no formal test of interaction was made, we also undertook prespecified exploratory analyses to investigate the effect of intervention stratified by age, sex, and anaemia status at baseline. The effect of IPT on anaemia did not differ by age-group (data not shown), but the effect in girls was slightly greater than in boys (data not shown). An increase in mean haemoglobin was seen in all subgroups of children, including those who were not anaemic at baseline (adjusted difference 7.42 g/L, 95% CI 3.05–11.79; $p=0.0018$).

At follow-up, scores for sustained attention were higher in the IPT intervention group than among controls for the counting sounds test (adjusted mean difference 1.80 [0.19–3.41; $p=0.03$; table 5) and the code transmission test (adjusted mean difference 6.05 [2.83–9.27; $p=0.0007$). The effect size was 1.22 (95% CI 0.003–0.35) in the counting sounds test and 0.86 (0.09–0.88) in the code transmission test. There was no difference in mean score for inattentive or hyperactive-compulsive behaviours (table 5) or mean educational achievement test scores (table 6) between study groups.

Seven children died during the 12-month intervention period: two in the IPT intervention group and five in the placebo group. Cause of death was investigated, but could not be reliably ascertained in all cases. 23 serious adverse events were reported within 28 days after any

mass treatment (includes children admitted for observation): 19 in the intervention group (of which three were judged to be possibly associated with treatment) and four in the control group. The most common serious adverse events were problems of balance, dizziness, feeling faint, nausea, or vomiting, which all occurred within 5 h of treatment. There was only one report of a severe skin reaction, which occurred in the placebo group. A further 13 adverse events were graded as moderate: six in the intervention group and seven in the placebo group. Mild events, such as nausea, headache, and pruritis, were more frequent among children receiving active drugs than among controls (49 and 33 reports, respectively).

Discussion

This trial has shown that school-based delivery of IPT once per term markedly reduced the prevalence of anaemia and asymptomatic parasitaemia in semi-immune schoolchildren in Kenya. We also show a beneficial effect of malaria treatment on sustained attention of schoolchildren. Although only 73% of enrolled children were followed up, there were no marked differences in background characteristics or follow-up rates between study groups, suggesting that treatment effects were not caused by sample bias. Children receiving IPT were less likely to complete the full 3-day regimen, possibly because of the bitter taste of amodiaquine, but there was little evidence that this introduced bias since the characteristics of children who received complete and incomplete treatment were similar. Additionally, twice yearly anthelmintic treatment was given to all children (intervention and control), reducing helminth infection and anaemia in both groups from initial baseline levels. The resultant similarities in levels of helminth infection between study groups at follow-up, as well as nutritional status, provide convincing evidence that the effect on anaemia was mainly caused by reductions in malaria parasitaemia.

Our findings are consistent with earlier observations that insecticide-treated bednet use is associated with reduced anaemia in adolescent schoolgirls,²² suggesting that malaria control could have an important role in preventing anaemia in school-aged children. The size of the protective effect of IPT against anaemia is markedly greater than the protective effects seen in previous trials of anthelmintic treatment.^{23–25} The effect is also comparable with, or larger than, reductions in the rates of anaemia seen following iron supplementation.^{26–29} Notably, previous trials often report that either young children or anaemic children benefit most from intervention. However, in our study the protective effect of the intervention against anaemia did not differ among age-groups, and significant improvements in mean haemoglobin concentrations were seen in children who were not classified as anaemic at baseline. This effect

	Placebo		IPT		p value	Difference in means (95% CI)
	Number of children tested	Mean score	Number of children tested	Mean score		
Intention-to-treat analysis						
Counting sounds (maximum score 20)*						
Crude†	378	15.41	433	16.01	p=0.048	0.60 (0.01 to 1.19)
(Range between schools; k=0.03)		(13.47–16.40)		(14.63–17.30)		
Observed–expected: adjusted for strata‡	378	–0.329	433	0.266	p=0.048	0.60 (0.01 to 1.19)
Observed–expected: fully adjusted§	328	1.405	351	3.208	p=0.030	1.80 (0.19 to 3.41)
Code transmission (maximum score 40)¶						
Crude†	368	23.28	423	27.20	p=0.019	3.92 (0.70 to 7.14)
(Range between schools; k=0.15)		(16.87–31.00)		(19.50–33.62)		
Observed–expected: adjusted for strata‡	368	–1.862	423	2.058	p=0.019	3.92 (0.70 to 7.14)
Observed–expected: fully adjusted§	323	0.572	342	6.624	p=0.0007	6.05 (2.83 to 9.27)
Teacher-rated score for inattentive or hyperactive-compulsive behaviours (maximum score 38)						
Crude†	137	11.67	126	10.90	p=0.543	–0.77 (–3.36 to 1.82)
Observed–expected: adjusted for strata‡	137	0.170	126	–0.729	p=0.481	–0.90 (–3.49 to 1.69)
Observed–expected: fully adjusted**	134	0.204	120	0.057	p=0.910	–0.15 (–2.81 to 2.52)
Per-protocol analysis						
Counting sounds (maximum score 20)*						
Crude†	272	15.48	209	16.14	p=0.097	0.66 (–0.13 to 1.45)
(Range between schools; k=0.02)		(13.14–16.33)		(13.00–17.70)		
Observed–expected: adjusted for strata‡	272	–0.255	209	0.407	p=0.097	0.66 (–0.13 to 1.45)
Observed–expected: fully adjusted§	238	1.403	173	3.530	p=0.068	2.13 (–0.17 to 4.42)
Code transmission (maximum score 40)¶						
Crude†	264	23.32	205	27.72	p=0.013	4.40 (1.01 to 7.80)
(Range between schools; k=0.16)		(15.60–31.20)		(17.86–33.40)		
Observed–expected: adjusted for strata‡	264	–2.155	205	2.249	p=0.013	4.40 (1.01 to 7.80)
Observed–expected: fully adjusted§	234	0.471	169	7.214	p=0.0016	6.74 (2.84 to 10.65)
Teacher-rated score for inattentive or hyperactive-compulsive behaviours (maximum score 38)						
Crude†	106	11.58	68	10.62	p=0.537	–0.96 (–4.11 to 2.19)
Observed–expected: adjusted for strata‡	106	–0.135	68	–1.499	p=0.381	–1.36 (–4.52 to 1.79)
Observed–expected: fully adjusted**	105	–0.019	67	–0.457	p=0.818	–0.44 (–4.33 to 3.45)
Placebo and IPT intervention arms both contained 15 schools. *Test included 20 counting sounds tasks, with up to 30 sounds per task. The total score was the number of times the sounds were counted correctly. †Crude estimates account for the cluster-randomised trial design. ‡Adjusted for stratified, cluster-randomised, trial design. §Fully adjusted for strata, age, sex, class, baseline haemoglobin concentration, and sustained attention score at baseline. Baseline haemoglobin concentration and baseline sustained attention scores were not available for all children. ¶ Test included two tests, in which children were required to record the two or three numbers, respectively, that preceded the code. Each test comprised 20 sets of code transmission targets. The total score was the number of times the target digits were correctly identified. Data available for children in 14 schools in each treatment arm in per-protocol analysis; and for 14 schools in placebo arm in intention-to-treat analysis. **Fully adjusted for strata, age, sex, class, baseline haemoglobin concentrations. Baseline haemoglobin was not available for all children. Since attention function was only assessed post-treatment, no adjustments could be made for attention at baseline.						
Table 5: Effect of IPT on cognition: attention in class						

Table 5: Effect of IPT on cognition: attention in class

could have been achieved through the clearance of asymptomatic infections that would otherwise go untreated, thereby providing a window for haematological recovery. Decreased rates of destruction and removal of parasitised red blood cells, and improvements in the rate of erythrocyte production in the bone marrow³⁰ during parasite-free periods might contribute to improvements in haemoglobin concentration and anaemia. Long-acting drugs, such as sulfadoxine-pyrimethamine, could also provide a period of prophylaxis immediately after treatment.³¹

Concerns that chemoprevention might impede the development of antimalarial immunity and lead to

rebound morbidity¹⁵ might be less relevant in the age-group studied here, especially under intense transmission where early exposure promotes rapid acquisition of immunity before reaching school age. Treatment at 4-month intervals permits reinfection, maintaining levels of exposure-dependent immunity. Studies undertaken after completion of the trial showed the IPT strategy to be well accepted by teachers, parents, and schoolchildren (data not shown). Few serious adverse events attributable to study medication were recorded, and most symptoms were mild and self-limiting. Nonetheless, their occurrence in healthy asymptomatic children is not desirable.

	Placebo		IPT		p value	Difference in means (95% CI)
	Number of children tested	Mean score	Number of children tested	Mean score		
Intention-to-treat analysis						
Social science exam: standard 6 (maximum score 39)*						
Crude†	240	16.20	263	16.27	p=0.951	0.07 (-2.36 to 2.50)
Observed-expected: adjusted for strata‡	240	-0.002	263	0.071	p=0.951	0.07 (-2.36 to 2.50)
Observed-expected: fully adjusted§	200	1.893	250	1.440	p=0.747	-0.45 (-3.32 to 2.41)
Social science exam: standard 7 (maximum score 34)*¶						
Crude†	198	14.78	232	15.60	p=0.305	0.83 (-0.80 to 2.46)
Observed-expected: adjusted for strata‡	198	-0.399	232	0.380	p=0.333	0.78 (-0.85 to 2.41)
Observed-expected: fully adjusted§	137	3.815	195	3.964	p=0.938	0.15 (-3.75 to 4.05)
Per-protocol analysis						
Social science exam: standard 6 (maximum score 39)*						
Crude†	167	16.26	119	16.66	p=0.774	0.40 (-2.46 to 3.26)
Observed-expected: adjusted for strata‡	167	-0.419	119	-0.017	p=0.774	0.40 (-2.46 to 3.26)
Observed-expected: fully adjusted§	144	1.583	116	1.193	p=0.784	-0.39 (-3.29 to 2.51)
Social science exam: standard 7 (maximum score 34)*¶						
Crude†	146	14.71	120	15.41	p=0.362	0.71 (-0.87 to 2.28)
Observed-expected: adjusted for strata‡	146	-0.606	120	0.018	p=0.421	0.62 (-0.95 to 2.20)
Observed-expected: fully adjusted§	105	3.856	103	3.512	p=0.867	-0.34 (-4.53 to 3.84)
Placebo and IPT intervention arms both contained 15 schools. *Total number of correctly answered questions in a multiple-choice exam, specific to curriculum taught in each year group. †Crude estimates account for the cluster-randomised trial design. ‡Adjusted for stratified, cluster-randomised, trial design. §Fully adjusted for strata, age, sex, teacher absenteeism, quality of schooling, and baseline haemoglobin concentration. Baseline haemoglobin concentration was not available for all children. Social science exams were not carried out at baseline. ¶Data available for children in 14 schools in the placebo arm.						
Table 6: Effect of IPT on educational achievement						

Malaria early in life has been shown to impair later cognitive performance^{32,33} and clinical malaria affects school performance.^{13,14} Our results show that asymptomatic infection can also affect cognitive performance and that treatment against asymptomatic malaria improves sustained attention. However, by contrast with the Sri Lankan study,¹⁴ we did not find an improvement in educational achievement. Mean scores were generally low, suggesting that examined knowledge improved insufficiently in both placebo and intervention groups for a difference between them to be detected. Other possible reasons include low statistical power (<20%) because of greater than expected school-level clustering of educational achievement scores, short duration of follow-up, and the limited number of schoolchildren tested. Clinical attacks are less common in our population, which might also explain the difference between this and the Sri Lankan study.¹⁴

The mechanism for the effect on cognition is not known, but it is possible that raised haemoglobin concentrations had a role in improving attention. There is strong evidence that iron-deficiency anaemia leads to impaired cognitive function,³⁴ although the cognitive effect of anaemia due to causes other than iron deficiency is less well understood.³² Among many school health and nutrition interventions previously assessed, only

iron supplementation³⁵ and malaria prevention (in Sri Lanka¹⁴ and the current study) have shown substantial improvements in cognitive function of around 0.5 SD or greater.³⁶

This large field trial, using a randomised design, enabled the effect of malaria on sustained attention to be demonstrated, and provides strong evidence of a link between asymptomatic malaria and cognition. We did not, however, do an extensive battery of cognitive tests, and cannot determine whether asymptomatic malaria affects other aspects of cognitive function. Neither did we examine the effect of clinical attacks or absenteeism on anaemia or cognitive function. In other settings where the incidence of clinical attacks in schoolchildren is higher, this could adversely affect school performance and absenteeism. Knowledge of the effect of malaria on school performance and education is far from complete, but our findings provide sufficient evidence to indicate that this warrants more attention.

School health programmes provide an effective vehicle to control anaemia and improve educational outcomes of school-aged children living in developing countries.³⁷ The pronounced effects of the IPT intervention on anaemia and malaria parasitaemia, and the effect on sustained attention, highlight the issue of the continued, and often unrecognised, malaria burden

among school-aged children in Africa and the potential of school-based programmes for tackling the problem.⁹ Our findings also illustrate the possible gains of integrating malaria control into broader school health programmes.³⁸ These results now need to be replicated in different epidemiological settings. Further research is also needed to investigate the operational feasibility of the approach, and any long-term educational benefits.

Contributors

SEC, MCHJ, BBAE, and SB designed the study. MCHJ developed the cognitive tests and MCHJ and LK coordinated data collection of the cognitive and educational data. BBAE and JKN were responsible for administrative logistics. SEC, JKN, JO, and CC coordinated delivery of the intervention and supervised data collection teams. JO was the clinical officer and CC was responsible for data management. SEC, MCHJ, BC, and SB developed the analysis plan, and BC analysed the data. SEC and SB wrote the manuscript, and all authors commented on the final draft.

Conflict of interest statement

We declare that we have no conflict of interest.

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